DETAILED ACTION

1. Applicant's amendment and response filed 12/28/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I and species of fragment of an immunoglobulin which is the variable region of a heavy chain, said variable region devoid of normal light chain interaction sites, and Applicant's election with traverse of the species of "labeled with a detectable label" that is "a radioactive label" in Applicant's response filed 1/23/06.

Claims 18-21, 25-27, 31-33, 35 and 51-54 read upon the elected species.

Applicant is reminded that upon consideration of the prior art, the search had been extended to include the species recited in instant claim 22, *i.e.*, "immunoglobulin or a fragment thereof according to claim 19, which has a constant region which is devoid of a CH1 domain."

Claims 18-22, 25-27, 31-33, 35 and 51-54 are presently being examined.

3. The terminal disclaimer filed on 12/28/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,005,079 has been reviewed and is accepted. The terminal disclaimer has been recorded.

4. The terminal disclaimer filed on 12/28/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 5,840,526 has been reviewed and is accepted. The terminal disclaimer has been recorded.

5. The terminal disclaimer filed on 12/28/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,765,087 has been reviewed and is accepted. The terminal disclaimer has been recorded.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 18-22, 25-27, 31-33, 35 and 51-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the disclosure as filed is as follows: "wherein said fragment consists essentially of" a variable region or part of the variable region of a heavy polypeptide chain, said variable region being devoid of normal light chain interaction sites. Applicant does not point to support for the claim amendment as is required by MPEP 2163.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 18-22, 25-27, 31-33, 35 and 51-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claims 18 and 51 are indefinite in the recitation of "consists essentially of a variable region of a heavy polypeptide chain" because it is not clear what is meant.

b. Claims 19 and 52 are indefinite in the recitation of "consists essentially of part of the variable region of a heavy polypeptide chain" because it is not clear what is meant.

With regard to both "a" and "b" above, it is not clear by the recitation of the transitional phrase "consists essentially of" "a variable region of a heavy polypeptide chain" (in "a") or "part of the variable region of a heavy polypeptide chain" (in "b") what the said transitional phase opens the invention to, *i.e.*, which are the unlisted ingredients that do not materially affect the basic and novel properties of the invention and what those said properties are.

10. For the purpose of prior art rejections, the filing date of the instant claims 18-22, 25-27, 31-33, 35 and 51-54 is deemed to be the filing date of the instant application, *i.e.*, 1/5/04, as the parent applications do not support the claimed limitation of the instant claims as enunciated at item #7 supra of this Office Action.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Ungar-Waron *et al* (Isr. J. Vet. Med. 1987, Vol. 43(3), pages 198-203, IDS reference) as evidenced by Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference), Roux *et al* (PNAS USA 1998, Vol. 95, pages 11804-11809, IDS reference), WO 94/25591 (Applicant's IDS reference in the Form-1449 filed 7/24/06), van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record), and EP 0739981 A1 (of record).

Ungar-Waron *et al* teach a 40 Kd IgG from Camelid serum and composition thereof. Ungar-Waron *et al* teach that when camel serum was precipitated using ammonium sulfate, separated by DEAE-Sephacel, subjected to ultrafiltration, and analyzed by IEP and by SDS-PAGE two bands of 155 Kd and 100 Kd were visualized under non-reducing conditions, the 100Kd band dissociating into the 40 Kd band under reducing conditions upon SDS-PAGE analysis (especially Results and Discussion sections).

Evidentiary reference Hamers-Casterman *et al* teach VHH (V for variable region of heavy chain) from *Camelid* (infected with trypanosomes) serum that bind a large number of antigens present in a ^{35}S methionine-labeled trypanosome lysate, said VHH consisting of heavy-chain VHH dimers devoid of light chains and lacking the CH1 domain that binds to the light chain. Hamers-Casterman *et al* teach that the two 100 Kd immunoglobulin fractions yield only heavy chains of 46 Kd and 43 Kd upon reduction (see entire article, and especially second paragraph of article).

Evidentiary reference Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers (especially page 11804, column 2, paragraph before Materials and Methods section).

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1 domain, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4). *WO 94/25591 teaches that this 100 Kd IgG like material is the same as taught by Ungar-Waron et al (the art reference cited in this rejection, see page 1 at lines 18-19 and page 4 at lines 31-32).*

Although the art reference Ungar-Waron *et al* does not teach that the 40 Kd IgG band from *Camelid* serum contains VHH lacking CH1 and devoid of light chains or binds antigens such as those recited in instant claim 53:

- evidentiary reference Hamers-Casterman *et al* teach the approximately 40 Kd size of the VHH lacking CH1 and devoid of light chains in *Camelid* serum upon reduction of the 100 Kd IgG that bind antigens in a lysate containing proteins, carbohydrates and nucleic acids from an infectious agent and that some *Camelids* have high anti-trypanosome titers,
- Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers, and
- WO 94/25591 teaches that the 100 Kd fraction of the art reference Ungar-Waron *et al* contains *Camelid* IgG heavy chains that lack light chains, lack the CH1 domain, and that these heavy chains bind antigens.
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Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains (page 38 at the first full paragraph at column 1). van der Linden *et al* teach that unique features of VHH include the absence of both immunoglobulin light chains and the CH1 constant domain, and that camelid VHH have been shown to retain immunoglobulin functions such as specific antigen binding (paragraph spanning pages 43-44).

With regard to the recitation of "said variable region being devoid of normal light chain interaction sites" in instant claims 18, 19, 51 and 52, although the art reference Ungar-Waron *et al* does not teach that the *Camelid* IgG comprises a variable region devoid of normal light chain interaction sites, the evidentiary reference van der Linden *et al* teach that the *Camelid* variable fragments of the heavy chain antibodies do not have the hydrophobic interface which is important in the formation of a functional classical antibody molecule that is composed of heavy and light chains. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference EP 0739981 A1 teaches that the superior solubility of Camelid VH domain along with its small size and amino acid sequence of the framework region that is very homologous to that of human, ensure a minimum of immunogenicity when administered to humans (especially page 11 at lines 14-23), *i.e.,* that it is "suitable for use in *in vivo* diagnosis" recited in instant claim 32.

However, claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight *per se*.

Claims 51 and 52 are included in this rejection because the art reference teaches partially purified and substantially purified fractions containing of IgG from *Camelid* sera, *i.e.,* a "composition comprising a fragment of an Immunoglobulin…"

Claims 33 and 35 are included in this rejection because the art reference teaches the antibody labeled with a protein stain, *i.e.,* a detectable label that is a chemical label.

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. The instant claims that recite "fragment thereof" are included in this rejection because the 40 Kd band taught by the art reference is a fragment of a divalent immunoglobulin that binds antigen as evidenced by WO 94/25591.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 12/28/07 on pages 8-9 at section 1.

The teaching of Ungar-Waron *et al* is of a 100 kD band that dissociates into a 40 Kd band under reducing conditions under SDS-PAGE analysis. The evidentiary references teach that the 100 Kd immunoglobulin fractions yield only heavy chains of the same size upon reduction, that the 100 Kd IgG in camel serum is composed of heavy chain dimers that are devoid of light chains that lack the CH1 domain, that the approximately 40 Kd molecules are IgG2 and IgG3 classes that lack the light chain. Evidentiary reference WO 94/25591 teaches that the 100 Kd IgG material is the same as taught by Ungar-Waron *et al*, thus establishing that the 40 Kd material taught by Ungar-Waron *et al* is a *Camelid* heavy chain devoid of light chains. Thus, the 40 Kd protein is a fragment of the 100 Kd protein that is a *Camelid* antibody comprised of two heavy chains devoid of light chains.

13. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Grover *et al* (Ind. J. Biochem. Biophys. 1983, 20(4): 238-240, IDS reference filed 7/24/06, of record) as evidenced by WO 94/25591 (IDS reference filed 7/24/06), Satija *et al* (Inf. Immun. 1979, 24(2: 567-570, of record), van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record), and EP 0739981 A1 (of record).

Grover *et al* teach camel IgG2 isotype polyclonal antibodies, including in reduced form. Grover *et al* teach that polyacrylamide gel electrophoresis of ammonium sulfate precipitated camel serum immunoglobulins was done as described by Satija *et al* in Inf. Immun. 1979, 24(2): 567-570, (especially pages 238-239 of Grover *et al*).

Evidentiary reference WO 94/25591 teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1, which in one IgG class might be structurally replaced by an extended hinge. WO 94/25591 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG3 fraction binding to Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, page 2 at lines 1-4).

Evidentiary reference Satija *et al* teach that polyacrylamide electrophoresis involved staining the gel with a solution of amido black in HAc (*i.e.,* labeled with a detectable label that is a chemical marker as recited in instant claims 33 and 35, respectively, materials and methods section).

Although the art reference Grover *et al* does not teach that the IgG2 istoype antibody from *Camelid* serum contains VHH lacking CH1 and devoid of light chains, or binds antigens such as those recited in instant claim 53, evidentiary reference WO 94/25591 teaches that the *Camelid* IgG2 heavy chains lack light chains and that these heavy chains bind antigens. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable fragments of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains (page 38 at the first full paragraph at column 1). van der Linden *et al* teach that unique features of VHH include the absence of both immunoglobulin light chains and the CH1 constant domain, and that camelid VHH have been shown to retain immunoglobulin functions such as specific antigen binding (paragraph spanning pages 43-44).

With regard to the recitation of "said variable region being devoid of normal light chain interaction sites" in instant claims 18, 19, 51 and 52, although the art reference Grover *et al* does not teach that the IgG2 istoype antibody from *Camelid* serum comprises a variable region that is devoid of normal light chain interaction sites, the evidentiary reference van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is devoid of the immunoglobulin light chain and that the variable fragments of these heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains. Therefore the claimed antibody appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the antibody of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference EP 0739981 A1 teaches that the superior solubility of *Camelid* VH domain along with its small size and amino acid sequence of the framework region that is very homologous to that of human, ensure a minimum of immunogenicity when administered to humans (especially page 11 at lines 14-23), *i.e.*, that it is "suitable for use in *in vivo* diagnosis."

However, claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 51 and 52 are included in this rejection because the art reference teaches a partially purified fraction containing of IgG from *Camelid* sera, *i.e.*, a "composition comprising a fragment of an Immunoglobulin…"

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's said arguments are of record in the amendment filed 12/28/07 on pages 9-11.

Applicant's argument concerns assignment by Grover *et al* of the *Camelid* immunoglobulins as IgG1, IgG2, IgM and IgA based upon shape, position and electrophoretic mobility on an IEF immunoelectrophoresis gel as proposed by Butler *et al* for various other ruminants. Applicant cites Butler *et al* (to which Grover *et al* refer) for describing the different bovine Igs and their characteristics and the correspondence of their molecular weights to conventional four-chain immunoglobulins. Applicant argues that based upon this, it can be concluded that the IgG2 seen in Grover *et al* are conventional, four-chain immunoglobulins that have light chains. Applicant argues that the instant claims as amended recite only fragments of immunoglobulins that consist essentially of variable regions of heavy polypeptide chains, or binding parts thereof, that are devoid of normal light chain interaction sites.

However, an IEF gel is not used to equate molecular weights of different proteins as is argued by Applicant in citing Butler *et al* who teach that bovine IgG2 has a molecular weight of 163 and the heavy chain has a molecular weight of 55-58. In addition, evidentiary reference WO 94/25591 A1 clearly teaches the presence of considerable amounts of IgG like material of 100 Kd in the serum of the camel and that these molecules are composed of heavy chain dimers and are devoid of light chains. WO 94/25591 A1 further teaches that these molecules bear an extensive antigen binding repertoire, and that camel heavy chain IgGs lack the CH1. WO 94/25591 A1 teaches that heavy chain IgGs are a feature of all *Camelids*. WO 94/25591 A1 teaches that by a combination of affinity chromatography on Protein A and Protein G, three quantitatively important fractions corresponding to subclasses of IgG can be isolated from the serum of camels, two of which contain molecules of about 100 Kd, which upon reduction yield only heavy chains of 46 Kd (IgG2 fraction binding only to Protein A) and 43 Kd (IgG2 fraction binding to Protein A and Protein G), and both classes lack the light chain completely (see entire reference, especially page 1 at lines 18-32, and page 2 at lines 1-4). The structure of the art fragment of an antibody is the same as the structure of the fragment of the antibody of the instant claims, said fragment being a heavy chain devoid of light chains, lacking a CH1 region, said fragment a portion of the 100 Kd protein that is comprised of a heavy chain dimer.

14. Claims 18-21, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Frenken *et al* (J. of Biotechnology, 2000, 78: 11-21).

Based upon Applicant's amendment of the instant claims and the change in priority date of said claims as enunciated at item #10 supra, the following new ground of rejection is set forth below.

Frenken *et al* teach VHH fragments of *Camelid* antibodies specific for a hapten, and that these fragments may be produced in a eukaryotic host cell such as the yeast *S. cerevisiae*. Frenken *et al* teach these fragments labeled with an enzymatic marker or with a chemical marker (see entire reference, especially abstract, introduction, sections 2.2 and 3.3 and discussion).

Claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 51 and 52 are included in this rejection because the art reference samples of culture media containing secreted VHH fragments, *i.e.,* a "composition comprising a fragment of an immunoglobulin..."

15. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Lauwereys *et al* (The EMBO Journal, 1998, 17(13): 3512-3520).

Based upon Applicant's amendment of the instant claims and the change in priority date of said claims as enunciated at item #10 supra, the following new ground of rejection is set forth below.

Lauwereys *et al* teach single chain *Camelid* antibodies, devoid of normal light chain interaction sites, as well as variable domain fragments of said antibodies, including wherein the fragments are labeled with a chemical marker (on SDS-PAGE) or with an enzymatic marker (in ELISA), or monomeric heavy chains of the Camelid IgG2 and IgG3 antibodies that are devoid of light chains, including labeled with a chemical marker (on SDS-PAGE) (see entire reference).

Claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 51 and 52 are included in this rejection because the art reference teaches a partially purified fraction containing monomeric fragments of the IgG heavy chain antibodies from *Camelid* sera, *i.e.,* a "composition comprising a fragment of an Immunoglobulin..."

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 18-22, 25-27, 31, 32 and 51-54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-27 and 33 of copending Application No. 11/350,900 in view of van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record). This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

This is a new ground of rejection is necessitated by Applicant's amendment of the claims filed 12/28/07.

The instant claims are drawn to "A fragment of an immunoglobulin…said fragment consists essentially of…", whereas the claims of '900 are drawn to an immunoglobulin, not a fragment. In addition, instant claims 18, 19, 51 and 52 recite "said variable region being devoid of normal light chain interaction sites, whereas the claims 18, 23, 24, 26 and 27 of '900 recite "heavy chain immunoglobulin(s)…naturally devoid of light chains."

van der Linden *et al* teach that that the IgG *Camelid* heavy chain antibody is [naturally] devoid of the immunoglobulin light chain. van der Linden *et al* further teach that the variable *fragments* of heavy chain antibodies (VHH) do not have the hydrophobic interface which is important in the formation of a functional "classical" antibody molecule, composed of heavy and light chains, *i.e.,* lack interaction sites for light chain binding. van der Linden *et al* further teach that the VHH fragments have affinity in the nanomolar range, similar to mouse monoclonal antibodies and possess similar specificity and increased stability. Van der Linden *et al* teach that VHH antibody fragments can be produced in high yield and can be used for antibodies in unexpected products and processes (see entire reference, especially page 38 at the first full paragraph at column 1, abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made antigen-binding VHH fragments of the antibodies recited in '900 as per the teaching of van der Linden.

One of ordinary skill in the art would have been motivated to do this in order to capitalize on the high affinity, specificity and stability of these fragments that van der Linden *et al* teach can be used in place of antibodies in unexpected products and processes.

The humanized immunoglobulin recited in claims 24 and 25 of copending '900 are obvious variants of the immunoglobulins of the instant claims. Claim 54 is included in this rejection because an immunoglobulin that specifically binds a protein on tumor cells is an obvious variant of an immunoglobulin. Claim 53 is included in this rejection because an immunoglobulin that specifically binds a protein, hapten, carbohydrate or nucleic acid antigen is an obvious variant of an immunoglobulin.

The VHH IgG2 isotoype recited in the claims of copending '900 are encompassed by the VHH of the instant claims (which encompass IgGg2 and IgGg3 isotypes) as evidenced by van der Linden *et al*.

Applicant's arguments of record (on page 11 at section 1) in the amendment filed 12/28/07 have been fully considered, but are not persuasive.

Applicant argues that the claims of US 11/350,900 are not yet allowed and therefore this rejection should be withdrawn if the instant claims are otherwise allowable. Applicant requests withdrawal of this rejection.

The instant claims are not allowable, thus the instant rejection stands.

18. Claims 33 and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-27 and 33 of copending Application No. 11/350,900 in view of van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record) as applied to claims 18-22, 25-27, 31, 32 and 51-54, and further in view of Harlow and Lane (of record). This is a provisional obviousness-type double patenting rejection.

Claims 33 and 35 are drawn to a VHH immunoglobulin or fragment thereof labeled with a detectable label (claim 33) that is a radioisotope, an enzymatic marker, or chemiluminescent marker (claim 35).

The combination of van der Linden *et al* and the claims of '900 have been discussed supra.

However, the said combination does not provide for the limitation in claims 18-27 of '900 of a VHH immunoglobulin that is labeled with a detectable label.

Harlow and Lane teach labeling antibodies with radioisotopes, enzymatic markers or flurochromes (*i.e.*, chemiluminescent markers) for the purpose of immunoassay (page 591).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have labeled the immunoglobulin fragments of the said combination of van der Linden *et al* and of '900 with the detectable labels taught by Harlow and Lane.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to prepare immunoglobulin fragments as per the combination of van der Linden *et al* and '900 that are suitable for immunoassay as taught by Harlow and Lane.

Applicant's arguments of record (on pages 11-12 at section 2) in the amendment filed 12/28/07 have been fully considered, but are not persuasive.

Applicant argues that the claims of US 11/350,900 are not yet allowed and therefore this rejection should be withdrawn if the instant claims are otherwise allowable. Applicant requests withdrawal of this rejection.

The instant claims are not allowable, thus the instant rejection stands.

19. The prior rejection of claims 18-22, 25-27, 31, 32 and 51-54 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,005,079 (of record) as evidenced by WO 94/25591 (of record), by an admission in the instant specification on page 13 at paragraphs 2-5, and as evidenced by van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record) is hereby WITHDRAWN in view of Applicant's Terminal Disclaimer filed 12/28/07.

20. The prior rejection of claims 33 and 35 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,005,079 (of record) in view of Harlow and Lane (of record) is hereby WITHDRAWN in view of Applicant's Terminal Disclaimer filed 12/28/07.

21. The prior rejection of claims 18-22, 25-27, 31-33, 35 and 51-54 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,840,526 (of record) as evidenced by an admission in the instant specification on page 13 at paragraphs 2-5 and by van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record) and WO 94/25591 (of record) is hereby WITHDRAWN in view of Applicant's Terminal Disclaimer filed 12/28/07.

22. The prior rejection of claims 18-22, 25-27, 31-33, 35 and 51-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,765,087 (of record) as evidenced by van der Linden *et al* (Biochimica et Biophysica Acta 1999, 1431: 37-46, of record) is hereby WITHDRAWN in view of Applicant's Terminal Disclaimer filed 12/28/07.

23. No claim is allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
Group 1640
Technology Center 1600
April 3, 2008

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644